Kidney International, Vol. 20 (1981), pp. 615–620

Renal hemodynamics and renal kinins after angiotensin-converting enzyme inhibition

BARBARA H. CLAPPISON, WARWICK P. ANDERSON, and COLIN I. JOHNSTON

Monash University Department of Medicine, Prince Henry's Hospital, and the Baker Medical Research Institute, Melbourne, Victoria, Australia

Renal hemodynamics and renal kinins after angiotensin-converting enzyme inhibition. The effect of the angiotensin-converting enzyme (ACE) inhibitor captopril on the renal kallikrein-kinin system and renal hemodynamics was studied in anesthetised dogs for 45 min after captopril administration. ACE inhibition was confirmed by increases in blood angiotensin I (AI) and plasma renin activity and a 20-fold decrease in sensitivity of the blood pressure and renal blood flow dose-response curves to AI. Captopril (1.5 mg · kg^{-1}, i.v.) led to an increase in renal blood flow of 56 ± 13 ml/min^{-1} ($P < .01$) despite a fall in mean arterial pressure of 17 ± 5 mm Hg ($P < 0.005$). Glomerular filtration rate did not change whereas the filtration fraction decreased ($P < 0.005$). The hypotension and renal vasodilation were accompanied by an increase in urinary kinin excretion ($P < .025$) but no acute change in circulating kinins or urinary kallikrein excretion. Urine volume and urinary sodium and potassium excretion increased. To determine the contribution of the renin-angiotensin system to these hemodynamic changes, we gave captopril to a further group of dogs during a continuous infusion of the competitive angiotensin II (AII) receptor antagonist sar^{1}ile^8-AII (2.5 μg/kg/min). Subsequent ACE inhibition was still associated with an increase in renal blood flow of 35 ± 17 ml/min^{-1} ($P < 0.05$), decrease with a mean arterial pressure by 11 ± 4 mm Hg ($P < 0.025$). These results suggest that ACE inhibition increases levels of intra-renal kinins and that decreased degradation of these tissue vasodilator peptides may contribute significantly to the acute renal vasodilation and hypotensive effect of captopril.

Hémodynamique rénale et kinines rénales après inhibition de l'enzyme de conversion de l'angiotensine. L'effet du captopril, inhibiteur de l'enzyme de conversion de l'angiotensine (ACE), sur le système kallicréine-kinine et l'hémodynamique rénale a été étudié, chez des chiens anesthésiés, pendant 45 min après l'administration de l'inhibiteur. L'inhibition de l'ACE a été confirmée par les augmentations de l'angiotensine I (AI) et de l'activité rénine plasmatique et par une diminution de 20 fois des courbes dose-résponse de la sensibilité de la pression artérielle et du débit sanguin rénal à l'AI. Le captopril (1,5 mg · kg^{-1} i.v.) a déterminé une augmentation du débit sanguin rénal de 56 ± 13 ml · min^{-1} ($P < 0,01$) malgré une diminution de la pression artérielle moyenne de 17 ± 5 mm Hg ($P < 0,005$). Le débit de filtration glomérulaire n'a pas changé et la fraction de filtration a diminué ($P < 0,005$). L'hypotension et la vasodilatation rénale ont été accompagnées d'une augmentation de l'excrétion urinaire de kinine ($P < 0,025$) observée sans changement des kinines circulantes ou de l'excrétion urinaire de kallicréine. Le débit urinaire et les débits d'excrétion de sodium et de potassium ont augmenté. Afin de déterminer la contribution du système rénine-angiotensine à ces modifications hémodynamiques du captopril a été administré à un autre groupe de chiens au cours d'une perfusion continue de l'antagoniste compétitif du récepteur de l'angiotensine II (AII), la sar^{1}ile^{-8}-AII (2,5 μg/kg/min). L'inhibition de l'ACE a encore été associée à une augmentation du débit sanguin rénal de 35 ± 17 ml · min^{-1} ($P < 0,05$) alors que la pression artérielle moyenne a diminué de 11 ± 4 mm Hg ($P < 0,025$). Ces résultats suggèrent que l'inhibition de l'ACE augmente les concentrations intra-rénales de kinines et que la diminution de la dégradation de ces peptides tissulaires vaso-dilatateurs peut contribuer significativement à l'effet du captopril de vasodilatation rénale aiguë et d'hypotension.

The ACE inhibitor captopril (SQ14,225) inhibits the conversion of angiotensin I (AI) to the pressor peptide angiotensin II (AII), and the degradation of the depressor peptide bradykinin (BK) to inactive fragments [1]. Circulating AI and renin activity increase after captopril is administered and circulating AII levels decrease [2–5]. Although conflicting results have been obtained for levels of circulating BK after ACE inhibition [3–9], changes in tissue levels of the renin-angiotensin system and kallikrein-kinin system have not been measured.

It is now known that the kidney possesses a kallikrein-kinin system located in the distal tubular segments [10, 11]. Furthermore, urinary excretion of kallikrein and kinins probably reflect this renal system because urinary and renal tissue kallikrein have been shown to be identical [12, 13] and circulating kinins filtered at the glomerulus are destroyed in the proximal tubule [14, 15]. It is therefore possible that captopril may act on this local tissue kallikrein-kinin system.

Both AII and BK influence renal blood flow, renal function, and renal sodium reabsorption. The ACE inhibitors teprotide (SQ20,881) and captopril have been reported to increase renal blood flow in dog and man [4, 5, 16, 17] though whether this is due to a decrease in AII or an increase in BK is unknown.

This paper reports the acute effects of ACE inhibition by captopril on the urinary excretion of kallikrein, kinins, electrolytes, and water in anesthetized dogs and the resultant changes in blood pressure and renal hemodynamics. To determine which of the changes were due to inhibition of the renin-angiotensin system, we repeated the ACE inhibition, in the presence of complete AII blockade, by an angiotensin receptor antagonist.

Methods

Mongrel dogs (21.6 ± 1.4 kg of body wt) on standard diet (sodium, about 110 mEq/day^{-1}; potassium, 80 mEq/day^{-1}) were

Received for publication November 4, 1980
and in revised form February 27, 1981

0085-2538/81/0020-0615 $01.20

anesthetised with sodium pentobarbitone (30 mg/kg, i.v.) and artificially ventilated. The femoral artery was cannulated for arterial blood pressure measurement, and the femoral and jugular veins were cannulated for infusions of saline, ^{3}H-inulin, and drugs. A saline load of 1 liter was administered over 90 min starting with surgery and continuing at 1 ml/min^{-1} for the rest of the experiment. Heart rate was measured by a tachygraph from the ECG signal and blood pressure by a Statham strain gauge transducer. The left kidney was exposed by an extraperitoneal flank incision, and the left renal vein was cannulated by a modification of the method of Herd and Barger [18] for the collection of blood samples. The left ureter was cannulated for timed collections of urine. GFR was calculated from ^{3}H-inulin clearance using 15-min urine collection periods. Renal blood flow was measured using a Biotronex electromagnetic flow meter around the renal artery. Urine for measurement of urinary kallikrein and kinins was collected into inhibitors of kinin degradation (2.5 mmoles 1,10-phenanthroline, 2 mmoles ethylene-diaminetetraacetic acid (EDTA), 3 mmoles sodium azide).

Group 1 (N = 9 dogs). After two consecutive 15-min control periods, captopril 1.5 mg/kg^{-1} in 10 ml of saline was given i.v. Three further 15-min experimental periods were studied. Blood samples were withdrawn from the renal vein and femoral artery at the beginning and end of each urine collection period. To confirm ACE inhibition, we performed blood pressure and renal blood flow dose-response curves to exogenous AI (50 to 5000 ng/kg^{-1}) before and 45 min after captopril.

Group 2 (N = 6 dogs). This group was studied with the same protocol as group 1 dogs but received saline instead of captopril.

Group 3 (N = 6 dogs). After control observations, these dogs were given a continuous infusion of 2.5 μg/kg/min of sar^{1}ile^8-AII, an AII receptor antagonist. Thirty minutes later during the continuous infusion of sar^{1}ile^8-AII, they were given captopril (1.5 mg/kg^{-1}) and studied in the same manner used for group 1. Angiotensin blockade by the receptor antagonist was confirmed by comparing the blood pressure and renal blood flow dose-response to exogenous AII (5 to 1000 ng/kg^{-1}) before and 100 min after the sar^{1}ile^8-AII infusion was started.

Hormone assays. Blood BK and AI were measured by radioimmunoassay from an ethanolic extract of blood following the procedure of Mashford and Roberts [19] as previously described [2]. A 5-ml blood sample was collected into 20 ml of ethanol, centrifuged, and the precipitate re-extracted with 20 ml of 75% aqueous ethanol. The supernatants were combined and divided into two equal parts, one of which was blown down, ether washed, and then blown to dryness. This extract was reconstituted in 0.1 M phosphate-saline-casein buffer (pH, 7.4) containing EDTA and neomycin, and assayed for AI. The remaining part of the ethanolic extract was loaded onto a 0.5-cm-×-7.5-cm CM-Sephadex C25 column equilibrated in 0.075 M ammonium acetate (pH, 5.0). The column was washed with this buffer, and the BK was eluted with 1.0 M ammonium acetate (pH, 7.0). The samples were lyophilized and reconstituted in 0.1 M Tris hydrochloric acid (pH, 7.4) containing EDTA and phenanthroline, and assayed for BK. Recovery of added BK was 84.2 ± 3.2% and was determined for each experiment.

Plasma renin activity was measured by the method of Johnston et al [20].

Table 1. Blood pressure and renal hemodynamic measurements in 9 dogs given captopril (1.5 mg/kg^{-1}) and in 6 dogs given saline[a]

	Control	Experimental	*P*
	Group 1: Captopril		
Mean arterial pressure, *mm Hg*	126 ± 5	109 ± 6	<0.01
Heart rate, *beats · min*$^{-1}$	119 ± 7	137 ± 6	<0.005
Renal blood flow, *ml/min*$^{-1}$	192 ± 40	247 ± 46	<0.01
Renal vascular resistance, *mm Hg/ml min*$^{-1}$	0.77 ± 0.17	0.49 ± 0.11	<0.01
GFR, *ml/min*$^{-1}$	43.0 ± 10.7	43.3 ± 12.8	NS
Filtration fraction	0.36 ± 0.05	0.30 ± 0.05	<0.005
	Group 2: Saline		
Mean arterial pressure, *mm Hg*	123 ± 5	128 ± 4	NS
Heart rate, *beats · min*$^{-1}$	105 ± 9	105 ± 11	NS
Renal blood flow, *ml/min*$^{-1}$	199 ± 60	201 ± 52	NS
Renal vascular resistance, *mm Hg/ml min*$^{-1}$	0.83 ± 0.17	0.84 ± 0.16	NS
GFR, *ml/min*$^{-1}$	44.4 ± 6.3	44.7 ± 7.7	NS
Filtration fraction	0.34 ± 0.01	0.33 ± 0.02	NS

[a] The control and experimental values are the average of two 15 minute periods. Values are the means ± SEM. Statistical significance for changes determined by paired Student's *t* test.

Urinary kallikrein was measured with an enzymatic assay. The BK generated from incubation of urine with dog kallikrein substrate was determined by radioimmunoassay [21]. A 5-μl urine sample was diluted to 150 μl with 0.1 M glycine buffer (pH, 9.0) and incubated with 100 μl of purified dog kallikrein substrate for 5 min at 37° C. The reaction was stopped with 500 μl of ethanol, and the supernatant was assayed for BK. The urine was radioimmunoassayed directly for kinins [22]. Lysyl-BK and methionyl-lysyl-BK crossreact 100% and 90%, respectively, in the assay, and urinary kinins are expressed as total kinins excreted for each urine collection period.

Urinary electrolytes. Sodium and potassium were measured using a flame photometer.

Statistics. The results are presented as the mean ± SEM. The statistical significance of the changes were tested using the paired or unpaired Student's *t* test or analysis of covariance [23].

Results

Converting enzyme inhibition. Following captopril administration, there was a significant rise in blood AI levels from 14.3 ± 2.9 to 91.3 ± 35.6 pg/ml^{-1} ($P < 0.05$) together with a rise in plasma renin activity from 0.86 ± 0.26 to 4.74 ± 1.81 ng AI/ml^{-1}/hr^{-1} ($P < 0.05$). The blood pressure and renal blood flow dose-response curves to exogenous AI following captopril were shifted 20-fold to the right.

Blood pressure and renal hemodynamic changes after captopril. The changes in mean arterial pressure, heart rate, renal blood flow, renal vascular resistance, GFR, and filtration fraction in the dogs given captopril (group 1) or saline (group 2) for the control periods and for the experimental periods 15 min after captopril are shown in Table 1. No significant change occurred in any of these parameters in group 2 dogs given

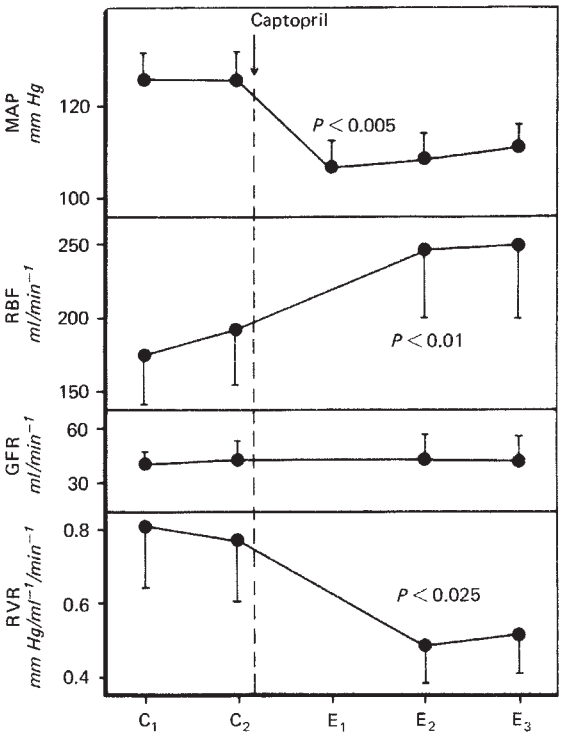

Fig. 1. *Changes in mean arterial pressure (MAP), renal blood flow (RBF), GFR, and renal vascular resistance (RVR) for group 1 dogs given captopril.* C_1 and C_2 denote 15-min control periods prior to administration of captopril. E_1, E_2, and E_3 denote 15-min experimental periods immediately following captopril. Values are the means ± SEM.

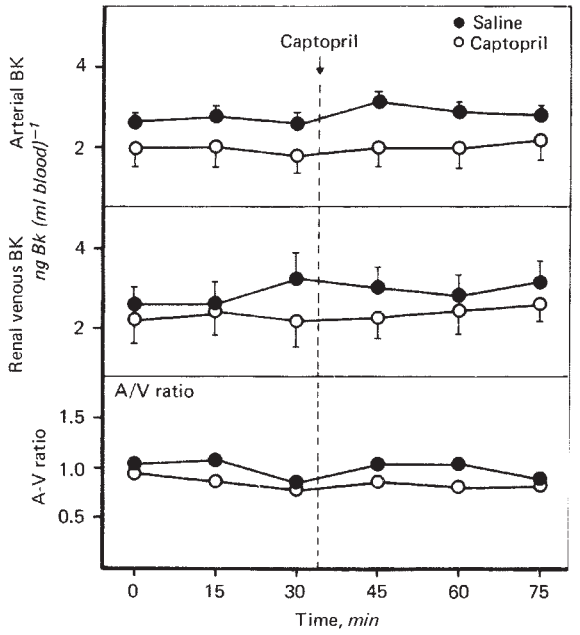

Fig. 2. *Circulating bradykinin levels before and after captopril for groups 1 and 2.* Values are the means ± SEM.

vehicle alone. The changes in the captopril-treated dogs for all the collection periods is illustrated in Figure 1. Captopril in these sodium-replete anesthetized dogs caused a sustained fall in arterial blood pressure of 17 ± 5 mm Hg but a significant increase in renal blood flow of 56 ± 13 ml/min^{-1} and a fall in calculated renal vascular resistance of 36%. There was no change in GFR, and the filtration fraction fell significantly.

Changes in circulating bradykinin after captopril. The circulating bradykinin levels before and after captopril are illustrated in Figure 2 for groups 1 and 2. Neither arterial nor renal venous levels changed with ACE inhibition, and thus the A/V ratio remained close to one.

Changes in urinary volume, sodium, potassium, kinins, and kallikrein. Captopril caused a significant diuresis and increase in potassium excretion after 30 min and a more gradual increase in sodium excretion (Table 2). Group 2 dogs showed no alteration in urinary volume, sodium or potassium excretion. The urinary excretion of kinins increased significantly in the captopril-treated dogs (Fig. 3). Only small changes occurred in kallikrein excretion, and the changes did not significantly parallel the kinin changes ($P > 0.25$, analysis of covariance). The excretion of these substances did not change in the group 2 dogs given saline.

Effects of sar^{1}ile^8-angiotensin II. Following AII blockade with 2.5 μg/kg^{-1}/min^{-1} of sar^{1}ile^8-AII, the renal vasoconstrictor dose-response curve to exogenous AII was markedly shifted 1000-fold to the right, requiring more than 250 ng AII/kg^{-1} to cause any decrease in renal blood flow or rise in blood pressure. Infusion of sar^{1}ile^8-AII increased arterial blood pressure by 20 ± 3 mm Hg, and renal blood flow fell by 48 ± 12 ml/min^{-1}, reflecting the vascular agonist action of the competitive antagonist.

Captopril during sar^{1}ile^8-AII infusion. The effect of captopril during the continuous infusion of 2.5 μg/kg^{-1}/min^{-1} of sar^{1}ile^8-AII on mean arterial pressure, renal blood flow, GFR, and renal vascular resistance are illustrated in Figure 4. Despite angiotensin blockade, renal blood flow again increased significantly by 35 ± 17 ml/min^{-1} ($P < 0.05$), and mean arterial pressure fell significantly by 11 ± 4 mm Hg ($P < 0.025$). Renal vascular resistance decreased by 22%, and the GFR again remained constant. Although these changes were less than that caused by captopril in group 1 dogs, the changes in renal blood flow and mean arterial pressure after ACE inhibition in groups 1 and 3 dogs were not significantly different.

Urinary kinin excretion increased in five out of the six sar^{1}ile^8-AII-treated dogs, the mean excretion increasing from 32.3 ± 8.5 to 41.1 ± 10.7 ng/min^{-1}. Captopril caused increases of 8, 16, 18, 48, and 120% in these dogs, but the mean increase was not statistically significant. In one dog in which kinin excretion fell (−21%), renal blood flow did not change. Urinary kallikrein excretion showed a transient increase from 10.5 ± 1.9 to 13.3 ± 2.7 μg BK/ml^{-1}/hr^{-1} ($P < 0.05$) but returned to control levels within 45 min. There was, however, no significant diuresis, natriuresis, or kaliuresis after captopril in the presence of AII blockade.

Discussion

ACE inhibition with captopril caused an increase in urinary excretion of kinins. This could reflect changes in filtered kinins or changes in intrarenal generation. Although no renal extraction or release of BK after captropril could be demonstrated in

Table 2. Changes in urine parameters in 9 dogs of group 1 given captopril[a]

	Control	Captopril		
		Exp. 1	Exp. 2	Exp. 3
Urine volume, ml/min^{-1}	0.70 ± 0.10	1.04 ± 0.14	1.13 ± 0.12[b]	1.08 ± 0.18
Sodium excretion, $\mu Eq/min^{-1}$	161 ± 21	217 ± 47	237 ± 49	236 ± 63
Potassium excretion, $\mu Eq/min^{-1}$	25 ± 3	29 ± 6	31 ± 5[b]	30 ± 6

[a] Each urine collection period was 15 min and the control value is the average of the 2 control periods. Values are the means ± SEM.
[b] $P < 0.05$.

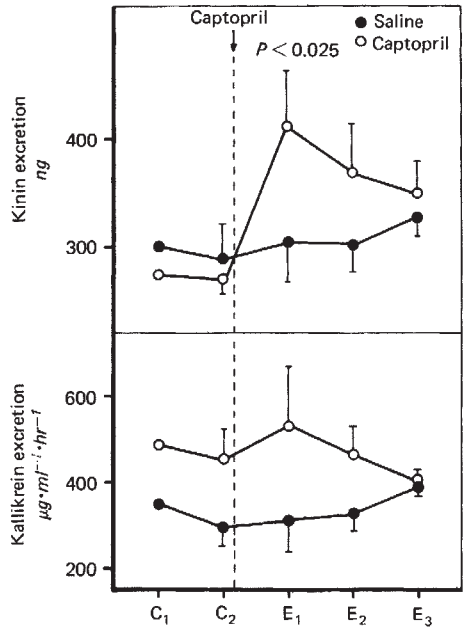

Fig. 3. *Urinary excretion of kinins and kallikrein before (C and C_2) and after (E_1, E_2, and E_3) captopril for groups 1 and 2.*

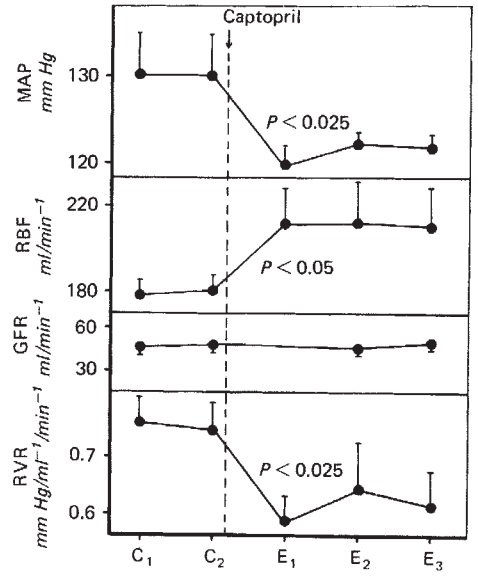

Fig. 4. *Changes in mean arterial pressure (MAP), renal blood flow (RBF), GFR, and renal vascular resistance (RVR) for group 3 dogs given captopril during infusion of sar^1ile^8-AII, 2 to 5 μg/kg/min.* C_1 and C_2 denote 15-min control periods prior to administration of captopril. E_1, E_2, and E_3 denote 15-min experimental periods immediately following captopril.

this study, BK has been shown to be filtered by the kidney [16]. Ward et al [14] reported high concentrations of kininases, including converting enzyme or kininase II, in the brush border of the proximal tubule, suggesting this is a major site of peptide inactivation for extrarenal kinins. Carone et al [24] found that when ^{3}H-BK was perfused into the proximal tubule only BK metabolites were excreted in the urine, whereas when perfused into the distal tubule 98% was recovered in urine. Captopril may act to inhibit the kininase II in the proximal tubule and thus increase urinary kinin excretion, but Nasjletti, Colina-Chourio, and McGiff [16] could not demonstrate increased urinary kinin excretion after BK infusion, even after ACE inhibition with SQ20881. Alternatively, kinins generated intrarenally from renal kallikrein, which has been localized in the distal tubular cells [10, 11], may be protected from degradation by ACE inhibition, and increased excretion in the urine may reflect these increased cellular levels of kinins. Ørstavik, Gautvik, and Nustad [25] have demonstrated that kallikrein is capable of being transported across an epithelial barrier, and kallikrein has been found in renal lymph [26], supporting the possibility of intrarenal transport. Kinins may also pass from these cells into the renal interstitium and vasculature and thereby influence renal hemodynamics. Olsen and Arrigoni-Martelli [27] also found urinary kinin excretion increased after captopril administration in conscious dogs.

Reported changes in levels of circulating BK after ACE inhibition have varied. Williams and Hollenberg [4] and Swartz et al [6] found small transient increases in plasma BK levels in sodium-deplete hypertensive patients infused with the ACE inhibitor SQ20881 but no significant changes in normotensive subjects. McCaa, Hall, and McCaa [5] found increased levels of blood kinins after a few days of treatment with SQ14225 in sodium-deficient dogs, whereas Hulthen and Hokfelt [7] reported transiently decreased BK levels in hypertensive patients. The failure to detect any change in blood BK levels after captopril administration in this study is in agreement with the results of Hollenberg et al [8], Matthews and Johnston [9] and Miller and Johnston [3], who all reported no significant change in circulating BK after ACE inhibition in hypertensive and normal man. The factors influencing circulating BK have not been defined, however, and the physiologic significance of blood BK is not known. Furthermore, ACE (kininase II) is not

the only degradative pathway for BK, and compensatory increases in other kininases may occur after ACE inhibition.

Captopril also caused a marked increase in renal blood flow despite a fall in mean arterial pressure. This renal vasodilation could have been caused by either the decreased levels of the vasoconstrictor AII or increased levels of the vasodilator BK, both a consequence of ACE inhibition. Thus, to eliminate the effect of decreasing levels of AII after captopril, dogs were pretreated with the competitive AII receptor antagonist sar^{1}ile^8-AII. But, captopril still caused hypotension and renal vasodilation although the changes were slightly less than they were in untreated dogs. This suggests that factors other than a decrease in the activity of the renin-angiotensin system contributed to these changes. Increased levels of intrarenal kinins may have mediated the changes, and the demonstration of increased urinary kinins after captopril independent of urinary kallikrein changes supports this idea. Both BK and lysine-BK have been previously shown to be potent renal vasodilators [16, 28].

Swartz et al [6] reported that infusions of AII after ACE inhibition restored mean arterial pressure to control levels but that the plasma AII levels achieved were higher after 30 min than control levels, suggesting that some other factor such as BK may also be responsible for the hypotensive response to ACE inhibition. McCaa [29] in long-term studies found, however, that infusions of AII at 5 ng/kg^{-1}/min^{-1} restored mean arterial pressure to almost normal levels after 3 days. Thurston and Swales [30], Jandhyala, Washington, and Lokhandwala [31] and Vollmer et al [32] have all found that pretreatment with the AII competitive antagonist saralasin did not prevent a fall in blood pressure after captopril, but they did not measure renal hemodynamics or kinin levels.

Wong and Zimmerman [33] have also studied the effect of captopril after AII blockade with saralasin. They used nonhypotensive hemorrhage as a prior stimulus to the renin-angiotensin system in anesthetized dogs and, in this renin-activated state, hemorrhage following saralasin was associated with a marked increase in renal blood flow, which captopril did not further increase. It is noteworthy, however, that in three of the eight dogs studied there was a 10 to 30% further increase in renal blood flow after captopril. In the other five dogs, the renal blood flow was not changed or decreased, and so the overall change was not statistically significant. This result may reflect differences in the response to captopril dependent on varying levels of activation of the renin-angiotensin system. The authors suggested that kinin potentiation may be responsible for the renal blood flow increases after captopril that were observed in some dogs. The diminished response to captopril in the sar^{1}ile^8-AII-treated dogs in our study may reflect the participation of the renin-angiotensin system, though the partial agonist properties of the antagonist do not allow one to draw this conclusion.

The results reported here suggest that bradykinin may play a significant role in the renal hemodynamic changes produced by acute ACE inhibition. The use of inhibitors of the kallikrein-kinin system during administration of captopril would further elucidate the role of the renal kallikrein-kinin system. But, the kallikrein inhibitors aprotinin and soy-bean trypsin inhibitor do not inhibit dog renal or urinary kallikrein in vitro (Moriwaki et al [34] and Clappison et al, unpublished observation) and a bradykinin receptor antagonist is not yet available.

This acute study over 45 min suggests that the short-term effects of ACE inhibition with captopril, as well as involving the renin-angiotensin system, are mediated in part by the kallikrein-kinin system.

Acknowledgments

These studies were supported by the National Health and Medical Research Council of Australia and the National Heart Foundation. Dr. Z. Horowitz (Squibb Institute) kindly provided the captopril for use in these studies.

Reprint requests to C. Johnston, Monash University, Department of Medicine, Prince Henry's Hospital, St. Kilda Road, Melbourne, Victoria, 3004, Australia

References

1. Ondetti MA, Rubin B, Cushman DW: Design of specific inhibitors of angiotensin-converting enzyme: new class of orally active antihypertensive agents. *Science* 196:441–444, 1977
2. Johnston CI, Millar JA, Casley DJ, McGrath BP, Matthews PG: Hormonal responses to angiotensin blockade: comparison between receptor antagonism and converting enzyme inhibition. *Circ Res* 46 (suppl 1):128–134, 1980
3. Millar JA, Johnston CI: Sequential changes in circulating levels of angiotensin I and II, renin and bradykinin after captopril. *Med J Aust* 2 (Suppl):xv–xvii, 1979
4. Williams GH, Hollenberg NK: Accentuated vascular and endocrine response to SQ20881 in hypertension. *N Engl J Med* 297:184–188, 1977
5. McCaa RE, Hall JE, McCaa CS: The effects of angiotension I-converting enzyme inhibitors on arterial blood pressure and urinary sodium excretion. *Circ Res* 43 (Suppl 1):32–39, 1978
6. Swartz SL, Williams GH, Hollenberg NK, Moore TJ, Dluhy RG: Converting enzyme inhibition in essential hypertension: The hypotensive response does not reflect only reduced angiotension II formation. *Hypertension* 1:106–111, 1979
7. Hultehn L, Hokfelt B: The effect of the converting enzyme inhibitor SQ20881 on kinins, renin-angiotensin-aldosterone and catecholamines in relation to blood pressure in hypertensive patients. *Acta Med Scand* 204:497–502, 1978
8. Hollenberg NK, Swartz SL, Passan DR, Williams GH: Increased glomerular filtration rate after converting enzyme inhibition in essential hypertension. *N Engl J Med* 301:9–12, 1979
9. Matthews PG, Johnston CI: Changes in endogenous circulating angiotensin and bradykinin after inhibition of converting enzyme (kininase II). *Med J Aust* 2 (suppl):xii–xv, 1979
10. Ørstavik TB, Nustad K, Brandtzaeg P, Pierce JV: Cellular origin of urinary kallikreins. *J Histochem Cytochem* 24:1037–1039, 1976
11. Carretero OA, Scicli AG: Renal kallikrein: its localization and possible role in renal function. *Fed Proc* 35:194–198, 1976
12. Nustad K: The relationship between kidney and urinary kininogenase. *Br J Pharmacol* 39:73–86, 1970
13. Moriya H, Matsuda Y, Miyazaki K, Moriwaki C, Hojima Y: Some aspects of urinary and renal kallikreins, in *Kininogenases-Kallikrein (Int Symp)*, edited by Haberland GL, Rohen JW, Suzuki T, New York, FK Schattauer Verlag, 1977, vol 4, p 29
14. Ward PE, Schultz W, Reynolds RC, Erdos EG: Metabolism of kinins and angiotensins in the isolated glomerulus and brush border of rat kidney. *Lab Invest* 36:599–606, 1977
15. Erdos EG: Angiotensin I converting enzyme. *Circ Res* 36:247–255, 1975
16. Nasjletti A, Colina-Chourio J, McGiff JC: Disappearance of bradykinin in the renal circulation of dogs. *Circ Res* 37:59–65, 1975
17. Murthy VS, Waldron TL, Goldberg ME: Inhibition of angiotensin converting enzyme by SQ14225 in anaesthetized dogs: hemodynamic and renal vascular effects. *Proc Soc Exp Biol Med* 157:121–124, 1978
18. Herd JA, Barger AC: Simplified technique for chronic catheterisation of blood vessels. *J Appl Physiol* 19:791–792, 1964

19. MASHFORD ML, ROBERTS ML: Determination of blood kinin levels by radioimmunoassay. *Biochem Pharmacol* 21:2727–2735, 1972
20. JOHNSTON CI, MENDELSOHN F, CASLEY DJ: Plasma renin determination employing a radioimmunoassay for angiotensin I. *Proc Aust Soc Med Res* 2:271, 1969
21. JOHNSTON CI, MATTHEWS PG, DAX EM: Effects of dietary sodium, diuretics and hypertension on renin and kallikrein, in *Systemic Effects of Antihypertensive Agents*, edited by SAMBHI MP, New York, Stratton International Medical Book Corporation, 1976, p. 323
22. SHIMAMOTO K, ANDO T, NAKAO T, TANAKA S, SAKUMA M, MIYAHARA M: A sensitive radioimmunoassay method for urinary kinins. *J Lab Clin Med* 91:721–728, 1978
23. SNEDECOR GW, COCHRAN WG: Analysis of Covariance, in *Statistical Methods*, edited by Iowa State University Press, Ames, Iowa, 1976, pp. 419–425
24. CARONE FA, PULLMAN TN, OPARIL S, NAKAMURA S: Micropuncture evidence of rapid hydrolysis of bradykinin by rat proximal tubule. *Am J Physiol* 230:1420–1424, 1976
25. ØRSTAVIK TB, GAUTVIK KM, NUSTAD K: Intraglandular transport of ^{125}I-glandular kallikrein in the rat submandibular salivary gland. *Acta Physiol Scand* 109:315–323, 1980
26. DE BONO E, MILLS IH: Simultaneous increases in kallikrein in renal lymph and urine during saline infusion. *J Physiol (Lond)* 241:127P–128P, 1974
27. OLSEN UB, ARRIGONI-MARTELLI E: The effects of kininase II inhibition by SQ14225 on kidney kallikrein-kinin and prostaglandin systems in conscious dogs. *Eur J Pharmacol* 54:229–234, 1979
28. WEBSTER ME, GILMORE JP: Influence of kallidin-10 on renal function. *Am J Physiol* 206:714–718, 1964
29. MCCAA RE: Studies in vivo with angiotensin I converting enzyme (kininase II) inhibitors, *Fed Proc* 38:2783–2787, 1979
30. THURSTON H, SWALES JD: Converting enzyme inhibitor and saralasin infusion in rats. *Circ Res* 42:588–592, 1978
31. JANDHYALA BS, WASHINGTON GF, LOKHANDWALA MF: Influence of inhibition of angiotensin I converting enzyme with SQ14225 on the arterial blood pressure of mongrel dogs. *Res Comm Chem Pathol Pharmacol* 22:257–265, 1978
32. VOLLMER RR, BOCCAGNO JA, HARRIS DN, MURTHY VS: Hypotension induced by inhibition of angiotensin-converting enzyme in pentobarbital-anaesthetised dogs. *Eur J Pharmacol* 51:39–45, 1978
33. WONG PC, ZIMMERMAN BG: Mechanism of captopril-induced renal vasodilatation in anaesthetized dogs after non-hypotensive hemorrhage. *J Pharmacol Exp Ther* 215:104–109, 1980
34. MORIWAKI C, MIYAZAKI K, MATSUDA Y, MORIYA H, FUJIMOTO Y, UEKI H: Dog renal kallikrein: purification and some properties. *J Biochem* 80:1277–1285, 1976